Supplementary Table 4. Classification of reported *NEFL* mutations according to ACMG/AMP standards and guidelines for the interpretation of sequence variants[1]

cDNA change	Amino acid change	Variant category[a]																		Variant classification[a]
		PVS1	PS1	PS2	PS3[b]	PS4	PM1[c]	PM2	PM3	PM4	PM5	PM6	PS4 mod.[d]	PP1 mod.[e]	PP1	PP2	PP3	PP4	PP5	
c.23C>T	p.Pro8Leu			+[g]	+		+	+					+				+			Pathogenic
c.23C>A	p.Pro8Gln				+		+	+			+						+			Pathogenic
c.23C>G	p.Pro8Arg				+		+	+				+	+	+			+			Pathogenic
c.22_23delCCinsAG	p.Pro8Arg		+				+	+							+		+			Pathogenic
c.48_60dup	p.Thr21Alafs*83				+		+	+									+			Likely pathogenic
c.64C>T	p.Pro22Ser				+		+	+					+	+						Pathogenic
c.64C>A	p.Pro22Thr				+		+	+			+				+					Pathogenic
c.65C>G	p.Pro22Arg						+	+			+				+		+			Likely pathogenic
c.268G>A	p.Glu90Lys			+[g]	+		+	+					+				+			Pathogenic
c.281T>C	p.Leu94Pro						+	+							+		+			Likely pathogenic
c.293A>G	p.Asn98Ser			+	+		+	+					+				+			Pathogenic
c.293A>C	p.Asn98Thr						+	+			+						+			Likely pathogenic
c.418G>T	p.Glu140*	+						+									+			Pathogenic
c.446C>T	p.Ala149Val				+			+												Likely pathogenic
c.556G>T	p.Glu186*	[f]						+									+			Uncertain significance
c.628G>T	p.Glu210*	+			+			+							+		+			Pathogenic
c.794A>G	p.Tyr265Cys							+							+		+			Uncertain significance
c.803T>G	p.Leu268Arg							+							+		+			Uncertain significance
c.803T>C	p.Leu268Pro							+					+		+		+			Likely pathogenic
c.932T>C	p.Leu311Pro							+									+			Uncertain significance
c.963_977del	p.Cys322_Asn326del							+		+					+		+			Likely pathogenic
c.995A>C	p.Gln332Pro				+			+					+		+		+			Pathogenic
c.998T>C	p.Leu333Pro							+									+			Uncertain significance
c.1001A>C	p.Gln334Pro							+									+			Uncertain significance
c.1007T>C	p.Leu336Pro							+									+			Uncertain significance
c.1150A>T	p.Ile384Phe						+	+							+		+			Likely pathogenic
c.1166A>G	p.Tyr389Cys						+	+							+		+			Likely pathogenic
c.1186G>A	p.Glu396Lys				+		+	+					+	+			+			Pathogenic
c.1261C>T	p.Arg421*	[f]						+									+			Uncertain significance[i]
c.1315T>A	p.Phe439Ile																			Uncertain significance
c.1319C>T	p.Pro440Leu							+					+		+		+			Likely pathogenic

(a) See reference 1 for category definitions and classification criteria. (b) *In vitro* or *in vivo* functional studies; see supplementary table 3 for references. (c) Variant located within a proposed mutational hotspot; see main text and figure 4 for details. (d) PS4 moderate: variant observed in two or more unrelated patients and absent in controls. (e) PP1 moderate. (f) Nonsense variants are not a clearly established mechanism of pathogenicity of autosomal dominant *NEFL*-related Charcot-Marie-Tooth disease (CMT); e.g., heterozygous carriers of p.Glu210* are asymptomatic,[2] p.Glu210* does not have a dominant-negative effect *in vitro*,[2] and there is no detailed information available about patients with CMT due to p.Glu186* and p.Arg421*.[3] (g) Reported as confirmed paternity.

REFERENCE

1. Richards S, Aziz N, Bale S, *et al*. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;**17**:405-24.

2. Yum SW, Zhang J, Mo K, Li J, Scherer SS. A novel recessive Nefl mutation causes a severe, early-onset axonal neuropathy. *Ann Neurol* 2009;**66**:759-70.

3. DiVincenzo C, Elzinga CD, Medeiros AC, *et al.* The allelic spectrum of Charcot-Marie-Tooth disease in over 17,000 individuals with neuropathy. *Mol Genet Genomic Med* 2014;**2**:522-9.